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Low plasma coenzyme Q10 levels and breast cancer risk in Chinese women

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Abstract

Background—Low circulating levels of Coenzyme Q₁₀ (CoQ₁₀) have been associated with increased cancer incidence and poor prognosis for a number of cancer types, while a recent prospective study observed a positive association for CoQ₁₀ with breast cancer risk.

Methods—We prospectively examined the association of plasma CoQ₁₀ with breast cancer risk in a nested case-control study of Chinese women within the Shanghai Women's Health Study (SWHS). Pre-diagnostic plasma samples were obtained from 340 cases and 653 age-matched controls and analyzed for total CoQ₁₀.

Results—A borderline significant inverse association for breast cancer incidence with plasma CoQ₁₀ level was observed using a conditional logistic regression model adjusted for age and age at first live birth, which became significant after elimination of cases diagnosed within one year of blood draw ($p_{\text{trend}} = 0.03$). This association was independent of menopausal status. Plasma CoQ₁₀ levels were also observed to be significantly associated with circulating γ -tocopherol ($r = 0.50$; $p < 0.0001$) and with α -tocopherol ($r = 0.38$; $p < 0.0001$) levels.

Conclusions—Circulating levels of CoQ₁₀ were generally low in this population and the observed association with breast cancer risk may be limited to those women with exceptionally low values.

Impact—This study reports an inverse relationship between circulating CoQ₁₀ and breast cancer risk, while the only other prospective study of CoQ₁₀ and breast cancer to date found a positive association. Lower levels of CoQ₁₀ in the SWHS population suggests that the two studies may not be contradictory and indicates a possible non-linear (U-shaped) association of CoQ₁₀ with risk.

Introduction

Coenzyme Q₁₀ (CoQ₁₀) was isolated and identified fifty years ago as an essential (rate-limiting) component of the mitochondrial electron transport system leading to ATP

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Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

production and is the only major lipid-soluble antioxidant synthesized by humans (1, 2). All mammalian cells are capable of synthesizing CoQ₁₀ (or closely related molecules) in a complex biosynthetic pathway involving the mevalonate pathway (also responsible for cholesterol and dolichol synthesis) and tyrosine, in a process dependent upon eight essential vitamins and nutrients (3,4). Mitochondrial energy production is essential for eukaryotic cell survival and CoQ₁₀ is a key molecule in all energy requiring processes, including proliferation, apoptosis, angiogenesis, and immune function (5–8), suggesting the potential for multiple roles in the initiation and progression of cancer. Despite the critical role of CoQ₁₀ in many cellular functions, its potential relationship with cancer development and progression has not received appropriate attention. Epidemiological or clinical studies of plasma or tissue CoQ₁₀ are rare in the literature and have involved limited numbers of subjects. Folkers, et al. (9), reported reduced circulating total CoQ₁₀ levels in breast cancer (n=17) and myeloma (n=15) patients. Palan et al., (10) in a cross-sectional study (n=230), reported an inverse association between cervical intraepithelial neoplasia and cervical cancer with total circulating CoQ₁₀, as well as with α -tocopherol (α T) and γ -tocopherol (γ T). Rusconi, et al. (11) reported a highly significant association between low plasma total CoQ₁₀ levels and metastasis and progression in 117 melanoma patients. Recently, in the largest epidemiologic study to date of CoQ₁₀ involving the Multiethnic Cohort, a positive association was observed for prediagnostic circulating total CoQ₁₀ and breast cancer risk in postmenopausal women (12).

Administration of CoQ₁₀ (as the oxidized quinone) to humans has been associated with a number of favorable clinical outcomes in the treatment of hypertension (13), heart failure (14), migraines (15), and myopathies associated with statin use (16). In the latter case there is growing concern for the long-term effects of statin use, resulting in decreased cellular CoQ₁₀ synthesis and Boudroux, et al. reported a non significant increasing risk for breast cancer in women as a function of length of time on statins (17). Positive effects have been reported for CoQ₁₀ in the treatment of breast cancer (18–20), however, these clinical studies were conducted on small numbers of patients and lacked adequate design.

Cellular and tissue levels of CoQ₁₀ decrease with age, and cellular levels below a critical threshold are incompatible with life (21). In contrast, plasma levels of CoQ₁₀ are reported by some to rise as a function of age (22), and are higher in postmenopausal women (23). Supplemental CoQ₁₀ increases circulating α -T levels in animals (24) and humans (25), however, the determinants of circulating CoQ₁₀ and its physiological regulation *in vivo* are unknown. The objective of the current study was to determine if an association exists between prediagnostic circulating CoQ₁₀ and breast cancer risk among Chinese women from the Shanghai Women's health Study (SWHS).

Materials and Methods

Study Population and Data Collection

The Shanghai Women's Health Study (SWHS) is a cohort of approximately 75,000 adult Chinese women between the ages of 40 and 70 in Shanghai, China (26). Subject recruitment was initiated in June 1997 and completed in May 2000. The cohort is being actively followed through a combination of record linkage with the files collected in the Shanghai Cancer Registry and Vital Statistic Unit and a biannual home visit. Nearly all cohort members were successfully followed, with the response rates for first in-person follow-up being 99.8% (2000–2002), second 98.7% (2002–2004), and third 96.7% (2004–2007). All possible matches identified by record linkage were verified by home visits. Medical charts from the diagnostic hospitals were reviewed to verify the diagnosis, and pathological characteristics of the tumor were recorded. Breast cancer cases were defined as women for whom breast cancer was the first cancer diagnosis (ICD-9, code of 174).

Blood samples were collected from 56,900 subjects (76% of the cohort) during the baseline survey period. Over an approximately average 7.5 years follow-up, the number of incident breast cancer cases initially available for analysis was 386 with two controls for each index case (772) selected randomly from the group of cohort members who were free of cancer at the time of cancer diagnosis of the index case. The controls were matched to the index case by age (± 2 years), menopausal status at baseline (yes, no), date of sample collection (± 30 days), time of sample collection (morning or afternoon), time interval after the last meal (± 2 hours), and recent antibiotic use (yes, no). After exclusion of samples with inadequate plasma available, incomplete matching information, or analytical interference, 340 cases and 653 controls were used in the subsequent analysis. Cases without controls or controls without cases were deleted from the analysis.

Laboratory Assays

Plasma samples were stored at -75°C , thawed and then aliquoted in a dark room for analysis. Plasma samples were extracted using hexane after addition of δ -tocopheryl laurate as an internal standard. The extracts were then stored at -80°C prior to subsequent analysis for total CoQ_{10} by HPLC (Model Spectra, ThermoFisher, San Jose, CA) with pre-column electrochemical oxidation (guard cell from ESA, Model 5020, Chelmsford, MA) and post-column UV detection at 275 nm (as described previously 12, 27). The separation was performed on a Gemini C18 analytical and guard column ($150\text{ mm} \times 2.0\text{ mm}$, $3\text{ }\mu\text{m}$ and $4\text{ mm} \times 3.0\text{ mm}$, $10\text{ }\mu\text{m}$, respectively; Phenomenex, Torrance, CA) with a mixture of sodium acetate trihydrate, glacial acetic acid, 2-propanol, hexane, and methanol. The range of inter-assay variability was 5 – 7 %. Plasma tocopherols were measured as described previously (28). Data for the distribution of CoQ_{10} levels among women was obtained from the current study and from another study (12) of CoQ_{10} and breast cancer utilizing the Multiethnic Cohort (MEC) performed by the same method in the same laboratory and provided by the authors of that study.

Statistical analysis

Conditional logistic regression, with matched sets as strata, was used to compute odds ratios (ORs) and 95% confidence intervals (CIs) whereby controls were matched to the index case by age, menopausal status at baseline, date of sample collection, time of sample collection, time interval after the last meal, and recent antibiotic use. CoQ_{10} levels were categorized into quintiles or quartiles based on the distribution of controls. The third quintile/quartile was chosen as the reference category to allow for a better comparison with the previous MEC study, in which the lowest tertile (median $\text{CoQ}_{10} = 668\text{ ng/ml}$) was used as a reference (12). In addition to matching variables, many potential confounding factors or effect modifiers have been obtained from survey or other studies (26,29). We conducted analyses to additionally adjust for age at first child birth, educational achievement, body mass index, regular physical activity (yes, no), number of full-term pregnancies, age at menarche, months of breast feeding, smoking status, and alcohol drinking. However, except for age at first live birth, adjusting for other covariates did not materially change the estimates. Stratified analyses were conducted by menopausal status and plasma concentration of γT (< 1948.9 ; > 1948.9). Sensitivity analyses were conducted by excluding those whose blood samples were collected within one year of cancer diagnosis to reduce the effects possible pre-clinical cases. *P* values of < 0.05 (2 sided probability) were interpreted as being statistically significant. Tests for trend were performed by entering the categorical variables as a continuous variable in the model. Statistical analyses were conducted using SAS statistical software (version 9.1; SAS Institute, Cary, NC).

Results

Baseline characteristics of patients and matched controls are shown in Table 1. Significant differences between cases and controls in the direction expected for this population were observed for education, age at menarche, age at first birth, months of breast feeding, and family history of breast cancer. Mean and median CoQ₁₀ levels overall were slightly lower in cases compared to controls (Table 2), however the difference was not statistically significant. When stratified by menopausal status, postmenopausal women were observed to have approximately 20% higher average circulating CoQ₁₀ levels compared to premenopausal women ($p = 0.07$ among controls).

As shown in Table 3, there was a borderline significant increased risk for all women in the lowest quintile of plasma CoQ₁₀ compared to the third quintile. After exclusion for cases diagnosed within one year of blood draw to reduce possible overt pre-clinical cases, a significant inverse association for plasma CoQ₁₀ with breast cancer risk was observed (p for trend = 0.03), with significantly increased risk for women in the 1st quintile (OR = 1.90; 95% CI, 1.14–3.16) relative to the third quintile of plasma CoQ₁₀. We found plasma levels of CoQ₁₀ significantly decreased with older age at first live birth ($p < 0.01$). After including age at first live birth in the model, the OR (95% confidence interval) for the lowest plasma level of CoQ₁₀ relative to the third quintile increased from 1.73 (1.07–2.80) to 1.90 (1.14–3.16) in the analyses excluding cases diagnosed within one year of blood draw. Stratification by menopausal status (Table 3) revealed similar trends by quartile with women in the lowest quartile of CoQ₁₀ at elevated risk relative to the third quartile for both pre and postmenopausal women (p for interaction = 0.40). However, sample size became smaller and results did not reach significance in stratified analyses. Adjustment for tocopherols did not change the observed associations.

As shown in Figure 1, plasma CoQ₁₀ levels were highly positively correlated with both plasma γ T ($r = 0.50$; $p < 0.0001$) and α T ($r = 0.38$; $p < 0.0001$) levels. Circulating γ T and α T levels were not correlated with one another. The distribution of values for plasma CoQ₁₀ for the women analyzed in the SWHS is shown in Figure 2. Comparison data from a similar study of postmenopausal women in the MEC (12) are plotted for comparison. Significantly greater CoQ₁₀ levels (approximately 60% higher) were observed in the MEC samples compared to the SWHS (means \pm SD were $1,007 \pm 387$ and 631 ± 254 ng/ml, respectively, $p < 0.00001$). Comparing only post menopausal women, the median CoQ₁₀ level in the MEC samples was 934 ng/ml compared to 633 ng/ml in the SWHS. In contrast, γ T levels in women from the SWHS (median = 1.95 μ g/ml) were nearly twice those observed for women in the MEC, where a median value of 1.07 μ g/ml was reported (12).

Discussion

In the SWHS we observed a significant inverse association for low circulating CoQ₁₀ with subsequent incidence of breast cancer for women whose breast cancer was diagnosed > one year after obtaining blood specimens with the highest risk associated with women in the lowest quintile of circulating CoQ₁₀. The results are consistent with previous reports of associations of low CoQ₁₀ with increased risk for various cancers and their progression (9–11). However, a recent prospective study of postmenopausal women utilizing the MEC found a significant positive association between plasma CoQ₁₀ and risk of breast cancer risk (12). That study (MEC) utilizing the same analytical laboratory as the current study found overall significantly higher levels of circulating CoQ₁₀ in a multiethnic American population compared to the current SWHS study (Figure 2). The median CoQ₁₀ for the reference tertile in the MEC study (668 ng/ml) was similar to the values for the SWHS cohort (536–629 ng/ml) where minimal risk was also observed. Significantly increased risk

for breast cancer was observed for the MEC study at CoQ₁₀ levels >1,000 ng/ml, a level found in very few women in the SWHS. A possible explanation reconciling these opposing results is that women at either extreme of CoQ₁₀ may be at increased risk for breast cancer. The Shanghai cohort encompasses the low end of what may be a U-shaped curve for CoQ₁₀ and the MEC study (12) captures the high end (Figure 2). Both prospective studies appear consistent in that women with circulating CoQ₁₀ levels in the range of 500–800 ng/ml have the lowest risk for developing breast cancer. It is unlikely that differences in sample collection or handling would account for any differences in CoQ₁₀ levels between these two populations as all CoQ₁₀ was oxidized to the stable quinone prior to analysis and measured as total CoQ₁₀ by the same method and laboratory.

Because cells are capable of synthesizing CoQ₁₀ endogenously, the question arises as to the source and physiological meaning of circulating CoQ₁₀. While the source and physiologic determinants of CoQ₁₀ in the blood are unknown, the close relationship between CoQ₁₀ and circulating tocopherols may provide some insight. The tocopherols were found to be highly associated with circulating CoQ₁₀ levels, suggesting either a causal relationship or a common regulatory mechanism. The mechanism of regulation of circulating tocopherol levels is also unknown, however, tocopherols, particularly γ T, are known to rise in response to inflammation (30, 31). The strong association between circulating CoQ₁₀ and tocopherols suggests that CoQ₁₀ level in the blood may also be mediated by systemic and/or localized inflammation (32). Increased release and/or retention of CoQ₁₀ into the circulatory system may, like γ T, be a response to processes such as inflammation, apoptosis, and cellular necrosis. Low circulating CoQ₁₀ levels may represent inadequate cellular levels, low inflammation, enhanced excretion, and/or inadequate immune function. The immune system can participate in cancer etiology in two opposing manners (33, 34). Chronic inflammation with an overactive immune system can result in cellular DNA damage and the development of tumors over time, while an inadequate immune response can lead to decreased immune surveillance and allow tumors to progress and metastasize.

The SWHS population appears to be quite unique (Table 1) with few participants who were ever smokers (1.5% for cases, 2.9% for controls), ever drinkers (2.1% for cases, 2.9% for controls), and current hormone therapy use (3.8% for cases vs 1.4% for controls), indicating that the population is quite unique relative to Western societies, thus limiting comparisons with the results of Chai, et al. where considerably higher smoking, alcohol and HRT use were reported (12). Differences in diet and supplement use may account for the stronger association observed between γ T and CoQ₁₀ in the SWHS. Unlike studies in U.S. populations, where α T supplementation is more prevalent, no inverse association was observed between circulating γ T and α T in women of the SWHS, which may account for the stronger association observed for both tocopherols with CoQ₁₀. In the study by Chai, et al. (12) the positive association between CoQ₁₀ and breast cancer risk was strongest in women with low γ T levels. In contrast, women in the SWHS were found to have generally higher γ T levels and lower CoQ₁₀ values (median γ -tocopherol of 1.95 μ g/ml in the SWHS vs 1.07 μ g/ml for the MEC women, 12). As was the case for CoQ₁₀, all tocopherols were measured in the same laboratory and the lower levels of γ T observed in the MEC are likely related to α T supplementation which significantly lowers γ T, but does not affect CoQ₁₀.

In conclusion, the current SWHS study, with relatively larger sample size and longer follow-up time suggests an inverse association for plasma CoQ₁₀ levels with breast cancer risk in Chinese women. The opposing relationships observed in the two prospective studies (SWHS vs the MEC), requires further research to verify the hypothesis that extreme levels of CoQ₁₀ in the plasma are indicators of risk. Additional study into the physiologic significance and regulation of plasma CoQ₁₀ and its relationship to tocopherols is needed. The present study does not address the role, if any, of supplemental CoQ₁₀ in the prevention and treatment of

cancer. Future intervention studies that can assess the physiological effects of supplementation will be necessary to identify the likely cause and effect relationships and determine the possible therapeutic benefits or potential harm of supplementation of CoQ₁₀.

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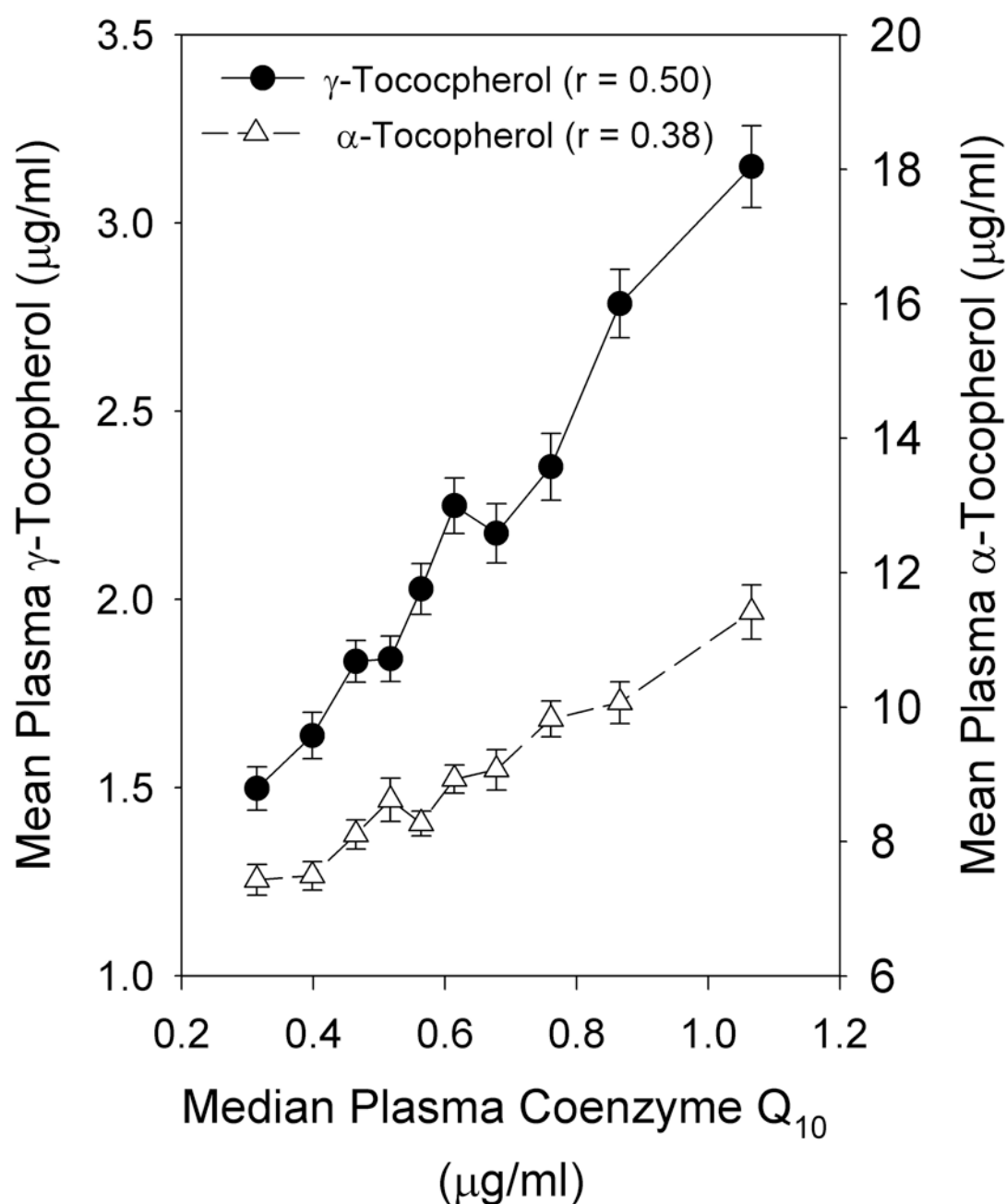


Figure 1.

Association of CoQ₁₀ with tocopherols in plasma. All subjects (n=1,113) were stratified by plasma CoQ₁₀ into deciles and α- and γ-tocopherol (mean ± SEM) plotted as a function of the median CoQ₁₀ level for each decile. Correlation coefficients were calculated for the association of each tocopherol with CoQ₁₀.

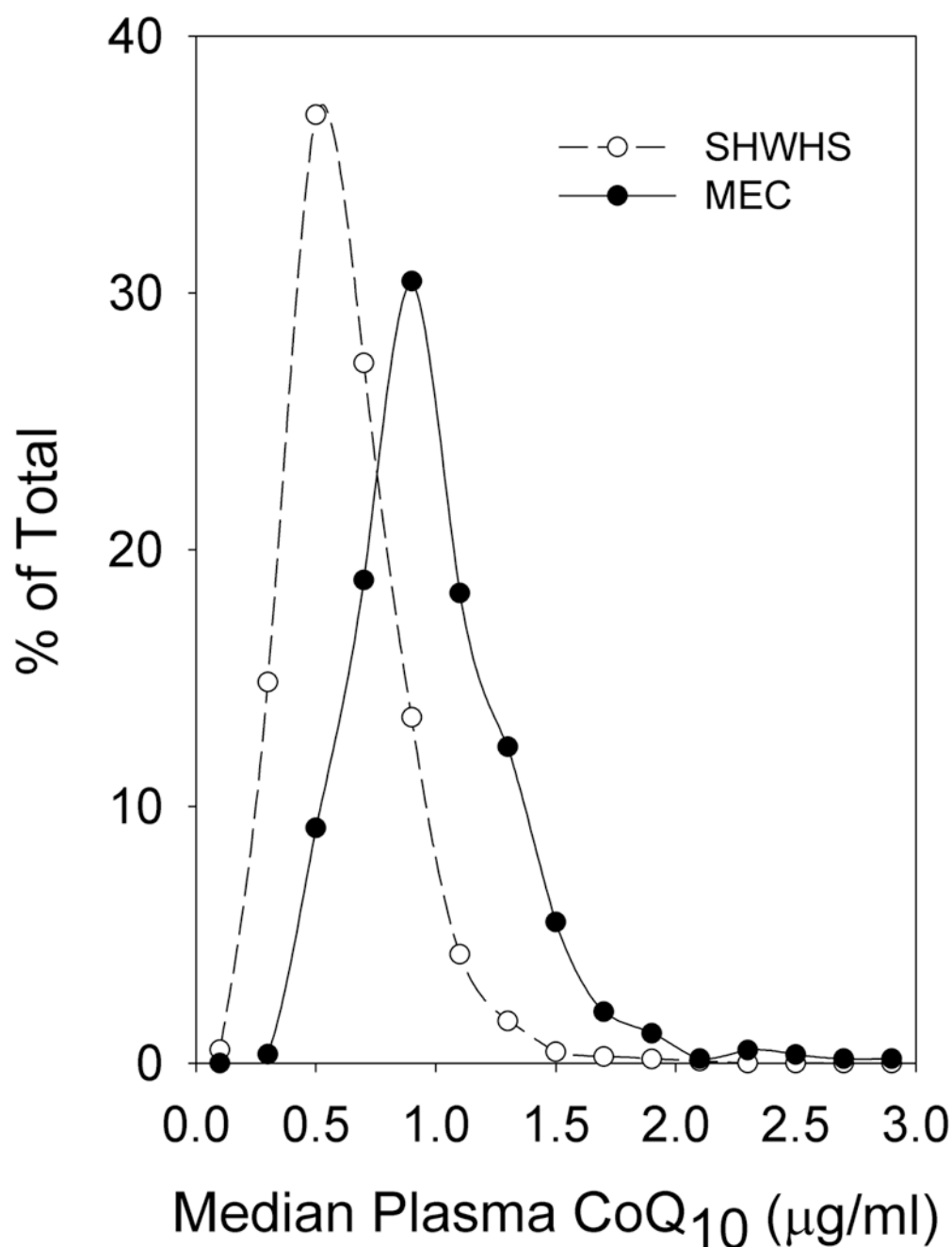


Figure 2.

Distribution of CoQ₁₀ levels found in cases and controls of the Shanghai Cohort: comparison with postmenopausal women from the Multiethnic Cohort study of CoQ₁₀ and breast cancer (12). The number of women with CoQ₁₀ values were determined for each 0.2 µg/ml increase in plasma CoQ₁₀ level and plotted as a percentage of the total number of women analyzed in the SWHS. For comparison, the distribution of plasma CoQ₁₀ levels in women analyzed for a study of CoQ₁₀ in the Multiethnic Cohort (12) are also shown.

Table 1

Characteristics of breast cancer cases and controls analyzed for CoQ₁₀ in a nested case-control study within the Shanghai Women's Health Study (SWHS), 1997–2006.

Characteristics	Cases (n=340)	Controls (n=653)	P- value [#]
Age at blood draw (years), mean (SD) *	52.4 ± 9.0	52.4 ± 9.0	0.15
Current hormone therapy use, n (%)	13 (3.8)	9 (1.4)	0.04
Education, n (%)			<0.01
Elementary and under	52 (15.3)	151 (23.1)	
Middle school	121 (35.7)	267 (40.9)	
High school	116 (34.2)	168 (25.7)	
College and above	50 (14.7)	67 (10.3)	
Body mass index (kg/m ²), mean (SD)			
All Women	24.2 ± 3.6	24.4 ± 3.3	0.29
Premenopausal Women	23.4 ± 3.2	23.6 ± 3.1	0.48
Postmenopausal Women	25.1 ± 3.7	25.3 ± 3.3	0.54
Physically active, n (%)	122 (35.9)	222 (34.0)	0.67
Nulliparous, n (%)	15 (4.4)	24 (3.7)	0.29
Number of full term pregnancies, mean (SD)	1.7 ± 1.1	1.8 ± 1.1	0.05
Age @ first child birth, mean (SD)	26.3 ± 4.1	25.6 ± 4.2	0.01
Age @ menarche, mean (SD)	14.8 ± 1.8	15.0 ± 1.7	0.03
Months of breast feeding	13.7 ± 15.6	16.3 ± 18.4	<0.01
Smoking status, n (%)			0.39
Never	335 (98.5)	634 (97.1)	
Former	0 (0)	1 (0.1)	
Current	5 (1.5)	18 (2.8)	
Mother or sister with breast cancer, n (%)	14 (4.12)	10 (1.5)	0.01
Alcohol use, n (%)			0.71
Never	333 (97.9)	634 (97.1)	
Former	1 (0.3)	2 (0.3)	
Current	6 (1.8)	17 (2.6)	
Deaths, n (%)	40 (11.7)	20 (3.1)	<0.01
Postmenopausal, n (%)	165 (48.5)	320 (49.0)	0.06

* SD Standard deviation

[#] Conditional logistic regression model for categorical variables or ANOVA test for continuous variables

Table 2

Comparison of plasma Q10 (ng/mL) levels between breast cancer cases and controls, a nested case-control study within the Shanghai Women's Health Study (SWHS), 1997–2006.

Plasma CoQ ₁₀ concentration (ng/mL)	Cases	Controls	P- value
All women (340 pairs)			
Mean ± SD	605.4 ± 241.0	619.2 ± 185.4	0.25 ^a
Median (25 th , 75 th)	560.0 (435.0, 728.0)	597.0 (500.0, 714.0)	0.16 ^b
All women with cases diagnosed > 1 year after blood draw (303 pairs)			
Mean ± SD	603.7 ± 242.8	622.9 ± 187.4	0.12 ^a
Median (25 th , 75 th)	553.0 (434.0, 739.0)	597.5 (502.5, 714.5)	0.09 ^b
Premenopausal women (171 pairs)			
Mean ± SD	544.6 ± 223.5	554.9 ± 153.0	0.38 ^a
Median (25 th , 75 th)	508.0 (382.0, 649.0)	554.0 (450.5, 644.0)	0.13 ^b
Postmenopausal women (169 pairs)			
Mean ± SD	667.0 ± 243.0	684.3 ± 192.9	0.45 ^a
Median (25 th , 75 th)	621.0 (494.0, 788.0)	649.5 (550.0, 789.0)	0.55 ^b

^aPaired test using log-transformed values for cases and the average of two matched controls.

^bPaired Wilcoxon signed rank test for cases and the average of two matched controls.

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Table 3

Odds ratios (ORs) and 95% confidence intervals (CI) for risk of breast cancer associated with plasma level of Q10 and stratified by menopausal status, a nested case-control study within the Shanghai Women’s Health Study (SWHS), 1997–2006.

Case-control pairs	OR (95% CI) by quintile of plasma concentration of CoQ10					P for trend
	Q1 ¹	Q2 ¹	Q3 ¹	Q4 ¹	Q5 ¹	
All women						
340	1.55 (0.97–2.48)	1.14 (0.72–1.80)	1.00 (Ref)	1.11 (0.71–1.74)	0.97 (0.60–1.60)	0.09
Women with cases diagnosed > 1 year after blood draw						
303	1.90 (1.14–3.16)	1.41 (0.87–2.30)	1.00 (Ref)	1.15 (0.71–1.87)	1.13 (0.66–1.91)	0.03
OR (95% CI) by menopausal status and quartile of CoQ10						
	Q1 ²	Q2 ²	Q3 ²	Q4 ²	P for Trend	
Premenopausal women ³						
All	1.62 (0.91–2.89)	1.38 (0.78–2.44)	1.00 (Ref)	1.15 (0.65–2.02)	0.16	
> 1 year	1.89 (1.01–3.54)	1.70 (0.91–3.16)	1.00 (Ref)	1.25 (0.68–2.32)	0.09	
Postmenopausal women ³						
All	1.35 (0.79–2.28)	1.04 (0.58–1.88)	1.00 (Ref)	0.96 (0.52–1.79)	0.24	
> 1 year	1.71 (0.95–3.09)	1.14 (0.60–2.15)	1.00 (Ref)	1.15 (0.59–2.23)	0.14	

¹ 20th, 40th, 60th and 80th percentiles were 429.0, 536.0, 629.0, and 796.0 ng/ml, respectively for all subjects.

² 25th, 50th, and 75th percentiles were 417, 537, and 665 ng/ml respectively for premenopausal women; and 517.5, 633, and 825 ng/ml respectively for postmenopausal women.

³ P for interactions was 0.40.

A conditional logistic regression model was used whereby controls were matched to the index case by age, menopausal status at baseline, date of sample collection, time of sample collection, time interval after the last meal, and recent antibiotic use and additionally adjusted for age at 1st live birth (continuous).